REMARKS

By this amendment, claims 12-18 have been canceled, and claims 1, 8 and 9 have been amended without any change of scope or intended meaning to clarify that the fluoromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether must positively contain an amount of 1,1,1,3,3,3-hexafluoroisopropyl alcohol. Support for the amendment is found, *inter alia*, in the original claim.

The rejection of claims 1-9 and 12-18 under 35 U.S.C. § 103(a) as obvious over Kawai, EP 0 703 450 A10, is respectfully traversed.

Applicants have discovered a process for purifying fluoromethyl 1,1,1,3,3,3-hexafluoroisopropyl ether (crude sevoflurane). According to the claimed process, crude sevoflurane containing not greater than about 0.25 wt.% of at least 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) is contacted with a basic aqueous solution. By starting with crude sevoflurane having this critical amount of HFIP, the HFIP can be removed from the crude sevoflurane.

Kawai does not teach that the amount of HFIP in the crude sevoflurane is limited to not greater than about 0.25 wt.%. In an attempt to remedy this deficiency, the Office Action points to Kawai's teaching that the ratio of HFIP to either hydrogen fluoride, (para)formaldehyde or sulfuric acid can effect the conversion of HFIP (page 3, lines 39-48). However, these ratios teach a skilled artisan absolutely nothing about the amount of HFIP in the crude sevoflurane.

For example, with respect to the HFIP:hydrogen fluoride ratio taught by Kawai, a skilled artisan learns only that an excess of hydrogen fluoride with respect to HFIP is necessary. But while the skilled artisan learns that the amount of hydrogen fluoride should be 1 to 20 times by mole of the amount of HFIP, he learns nothing about the actual amount of HFIP in the crude sevoflurane, which is a limitation required by the claims. In a similar vein, Kawai's ratios involving HFIP and (para)formaldehyde or sulfuric acid are unilluminating with respect to the amount of HFIP in the crude sevoflurane.

Kawai fails to teach or suggest that the initial impurity level of HFIP in sevoflurane is critical to a process for purifying the sevoflurane. Pointedly, Kawai fails to disclose or render obvious what the HFIP amount should be.

The claims further require that the basic aqueous solution includes a basic substance in an amount such that a chemical equivalent ratio of the basic substance to HFIP is not less than 1. In addition to not teaching or suggesting that the crude sevoflurane is required to have an HFIP content of not greater than about 0.25 % by weight, Kawai is also silent as to the claimed chemical equivalent ratio. In contrast to the assertion made in the Office Action, it would not have been obvious to select a chemical equivalent ratio of not less than unity based on the limited teaching of Kawai.

As set forth in MPEP § 2144.05:

> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation.

Kawai fails to identify the claimed chemical equivalent ratio much less teach that this ratio in any way affects the efficacy of HFIP removal from crude sevoflurane. Where the prior art does not recognize the parameter to be optimized as a result-effective variable, the claims cannot be held obvious. See *In re Antonie.*, 195 USPQ 6 (C.C.P.A. 1977).

In view of these deficiencies of Kawai, Applicants submit that a proper *prima facie* case of obviousness has not been established. Even assuming *arguendo*, however, that a *prima facie* case of obviousness had been made out, it would be effectively rebutted by the unexpected, superior results achieved by the critical ranges associated with the claimed process as set forth in the specification, Applicants' Declaration submitted with the Reply dated September 26, 2002, and Applicants' Declaration submitted concurrently herewith. See *In re Margolis*, 228 USPQ 940 (Fed. Cir. 1986).

Example 3 of the current specification establishes that the HFIP content in crude sevoflurane is dramatically reduced from 0.25 wt% to an amount less

than the detection limit of 1 ppm (i.e., 0.0001 wt%) by the alkali washing. One with skill in the art would appreciated that, if the initial HFIP content in the crude sevoflurane is less than 0.25 wt.%, the post-washing HFIP content would also be less than the detection limit of 1 ppm. This is an unexpected and surprising result in which the HFIP content is reduced to less than 1/2,500th of the original content, and is further confirmed by Experiment 3 of the Declaration filed September 26, 2002 and Experiments A, B and C of the Declaration of Matsue Kawamura under 37 C.F.R. 1.132 filed concurrently herewith.

The Kawamura Declaration submitted concurrently herewith sets forth facts establishing that the unexpected and surprising purification results are also achieved with an initial HFIP content of 0.20, 0.162 or 0.100 wt.%. This data is submitted in response to the assertion in the outstanding Office Action that purification data at a single HFIP content would be insufficient to allow one skilled in the art to ascertain a trend in the exemplary data.

Experiment A establishes that the HFIP content in crude sevoflurane is dramatically reduced from 0.20 wt.% to an amount less than the detection limit of 1 ppm by the alkali washing. This is an unexpected result in which the HFIP content is reduced to less than 1/2,000th of its original content.

Experiment B establishes that the HFIP content in crude sevoflurane is dramatically reduced from 0.162 wt.% to an amount less than the detection limit by the alkali washing. This is an unexpected result in which the HFIP content is reduced to less than 1/1,620th of its original content.

Experiment C establishes that the HFIP content in crude sevoflurane is dramatically reduced from 0.100 wt.% to an amount less than the detection limit by the alkali washing. This is an unexpected result in which the HFIP content is reduced to less than 1/1,000th of its original content.

Both Example 3 and the aforementioned Declaration Experiments A-C are commensurate with the scope of the claims and show that by causing crude sevoflurane containing not greater than about 0.25 wt.% HFIP to contact a basic aqueous solution, the HFIP can be removed from the crude sevoflurane.

Applicants submit that the Declaration data for HFIP contents of 0.25, 0.20, 0.162, and 0.100 wt.%, and the comparative data at an HFIP content of 4.91 wt.% is sufficiently detailed to allow one with skill in the art to ascertain a trend in the inventive data and reasonably infer from this trend the unexpected and superior results achieved over the claimed range. By using the process of the present invention, Applicants have demonstrated a reduction in the HFIP content of as much as 1/2500th the original value. The cited prior art does not teach or suggest a method of removing HFIP from crude sevoflurane that results in such a dramatic, unexpected reduction in the HFIP concentration.

Kawai teaches the purification of crude sevoflurane but fails to achieve the results of the present invention. To demonstrate this, Applicants produced crude sevoflurane in accordance with Example 1 of Kawai and washed this material with 4% sodium hydroxide aqueous solution in accordance with Example 6 of Kawai. The initial HFIP content in the crude sevoflurane produced according to the process of Kawai was 4.91 wt.%, which value lies outside of the claimed range of not greater than about 0.25 wt.% (see Experiment 1 of the Declaration filed September 26, 2002 and the results of Run 1). After washing this crude sevoflurane sample with the 4% sodium hydroxide solution, the HFIP content was reduced to 0.05 wt.%, which corresponds to a reduction of only about 1/100th of the original content (see Experiment 2 of the Declaration filed September 26, 2002).

Thus, in contrast to the inventive process, Example 6 of Kawai, which was identified in the Office Action dated March 27, 2002 to be the closest prior art of record, shows a reduction in the HFIP content to only about 1/100th of the pre-washing value.

In this direct comparison between the instant invention and the closest prior art of record, Applicants have demonstrated the superior and unexpected results that the amount of the reduction of the HFIP content by alkali washing is unexpectedly much greater when the HFIP content of the crude sevoflurane before the alkali washing is not greater than 0.25 wt.%. Notably, the fractional

reduction achieved using the process of the claimed invention (1/2500, 1/2000, 1/1620 and 1/1000) is at least an order of magnitude greater than the fractional reduction achieved using the process of Kawai (1/100).

In achieving this reduction, Applicants have shown that the amount of HFIP in crude sevoflurane is critical in obtaining high purity sevoflurane, and the effect of the claimed process in removing un-reacted HFIP depends on the initial concentration of un-reacted HFIP.

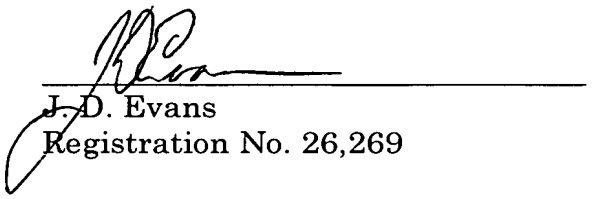
Applicants submit that the superior and unexpected results achieved using the process of the present invention effectively rebut any *prima facie* case of obviousness based on Kawai. In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned at (202) 624-2845 would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #038788.48236).

Respectfully submitted,

January 22, 2007



J. D. Evans
Registration No. 26,269

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE/MWR